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VERATRUM VIRIDE AND HEXAMETHONIUM IN THE TREATMENT OF SEVERE DIASTOLIC HYPERTENSION*†‡

EDWARD D. FREIS, M.D.

Adjunct Clinical Professor in Medicine, Georgetown University School of Medicine

DURING the past year we have been studying the effects of an intensive treatment program in a group of severe hypertensive patients who could be followed closely for prolonged periods. These patients were made available through the coöperation of Georgetown University, Mount Alto and Gallinger Municipal Hospitals, our own outpatient clinic at Georgetown University Hospital, and by referral of private patients by interested practicing physicians. All of the patients in this study have been selected on the basis of severity and almost all have been hospitalized for a period of preliminary observation and for institution of therapy. The majority of cases exhibited elevations of diastolic pressure persistently above 120 mm. of Hg even at hospital bed rest.

The reasons for making such a selection are that these severe cases represent the most urgent treatment problem, whereas patients with the more benign forms of the disease may and usually do live for many years without complications, and that, since in a high percentage of the severe cases death occurs within 5 years, it is easier to evaluate not only hypotensive responses but also success in preventing mortality.

VERATRUM VIRIDE

The plan of management has been as follows: The patients who did not respond after a preliminary period of observation with conservative treatment such as rest, reassurance and sedation, were given either Anatensol or Veriloid (purified extracts of Veratrum viride in tablet form) or a low sodium diet or both. If this therapy was successful it was further evaluated by the use of alternating placebo and treatment periods. If unsuccessful, sympathectomy has been carried

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‡ The portion of this article on Veratrum viride was submitted for publication, October 31, 1950; that on hexamethonium, May 3, 1951.

out in a few instances. In short, every effort has been made, using all the practical procedures at our disposal, to reduce the blood pressure to a more benign range.

I shall summarize several cases of severe hypertension so treated in order to indicate the manner in which therapy has been carried out and some of the results obtained thus far. The first is a 60-year-old man who entered the hospital because of increasing fatigue and mental confusion. The blood pressure averaged 220/140 during 5 days of rest in bed in the hospital (figure 1). The fundi revealed hemorrhages, exudates and definite papilledema of over 1 diopter.

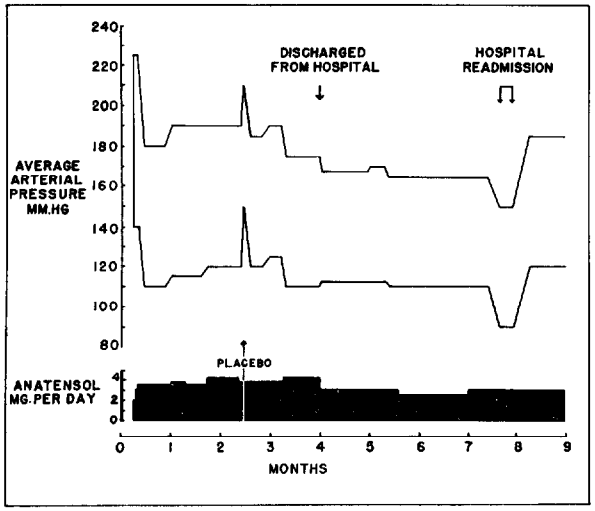

FIG. 1. Chart of the average arterial pressure (supine) and dosage of Anatensol of patient, L. E., a man aged 61 years. The recorded levels of arterial pressure represent averages of many individual readings for each period. See text for further details.

Renal function was impaired and the blood nonprotein nitrogen was 50 mg. per cent. The patient was placed on a regular diet without salt shaker and was given Anatensol,* an extract of Veratrum viride in rapidly increasing doses, which was followed by a fall in arterial pressure to 190/120. Nausea and vomiting due to the Anatensol were frequent, and the dosage had to be juggled considerably. Differences in doses of as little as $\frac{1}{4}$ of a tablet at times resulted in the difference between toxic vomiting and therapeutic effects. However, despite the frequency of nausea and vomiting the patient slowly improved, and within a month the papilledema had cleared and the blood nonprotein nitrogen was reduced to 40 mg. per cent.

There are several points worthy of note in this case. One is the long period of hospitalization lasting 3 months. This was necessitated by the continuously changing dosage requirements as judged by blood pressure changes and toxic reactions. These blood pressure recordings are averages of many readings. The actual pressures taken on the ward showed great fluctuation, hence requiring constantly changing minor dosage adjustments. The other point is the response to placebos. It is only by giving placebos under hospital observation that one can accurately judge the effect of the drug, and it is only in such severe cases that one can observe such a prompt and definite rise when placebos are given. After discharge from the hospital the patient has continued to improve very slowly. He has been forced to retire from work but is ambulatory and symptom-free. In fact, he has just returned from a month's vacation trip to northern Michigan. Episodes of nausea and vomiting due to the Anatensol are now infrequent, occurring about once or twice per month. I am quite certain that without frequent and close observation of the patient's response, constant readjustment of dosage in the first 3 months, persistence, and a certain degree of confidence in the treatment therapy with Anatensol would have long since been given up as a failure.

The next case (figure 2) is an example of the effectiveness of combining the 200 mg. sodium diet and veratrum extracts. This is a 32-year-old Negro taxi driver who entered the hospital because of headache, blurred vision, and easy fatigability. The blood pressure on admission was 250/150 mm. Hg but fell after admission to 180/120 mm. Hg under the influence of hospital bed rest. The optic fundi exhibited marked arteriolar

* A product of The Squibb Institute for Medical Research, New York, N. Y.

spasm with hemorrhages and exudates, but no papilledema. The heart size was normal, and renal function was good. The patient was given Veriloid,* and when the dosage was increased to 3 mg. 4 times per day the blood pressure fell promptly to 140/90. He was discharged from the

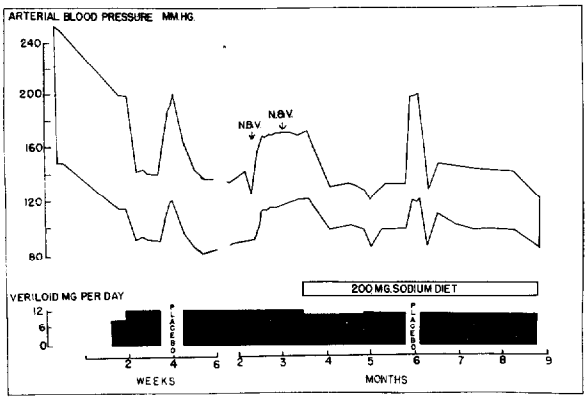

FIG. 2. Chart of arterial pressure (supine) and treatment of patient, R. C., a 31-year-old Negro. N. & V. signifies nausea and vomiting. See text for details.

hospital and returned to work but was seen daily in order to check his blood pressure and to question him concerning the development of toxic side-effects. He continued to do well despite return to full-time active employment as a taxi driver. When a placebo was given, there was a prompt rise in blood pressure with return of headache. It is important to point out that treatment with Veriloid would have been called a failure at the third month when it became impossible to regulate dosage without frequent attacks of nausea and vomiting. On the other hand, when diet was added the veratrum appeared to contribute to the effectiveness of the diet as can be noted by the moderate rise that occurred when the placebo was again substituted. He has been followed now for a total of 14 months, and his last blood pressure was 110/80. He has had no toxic reactions for the past 6 months.

This synergism of diet plus drug treatment seems to be an important general principle in the management of severe hypertension. In the unusual case, such as the first case described, veratrum alone appeared to maintain the patient's blood pressure in the benign range. In a greater percentage diet plus veratrum is essential to achieve this purpose, and in still others sympathectomy plus diet plus all that various types of drug treatment have to offer must be used together.

The next case illustrates the latter type of case in which every type of treatment was applied in combination (figure 3). The patient is a 28-year-old Negro government clerk. Renal and cardiac function were still good, and the fundi were only grade II. The blood pressure was remarkably fixed at a high level of 240/140 mm. Hg despite hospital rest and a rice diet followed by the low sodium diet. There was no response

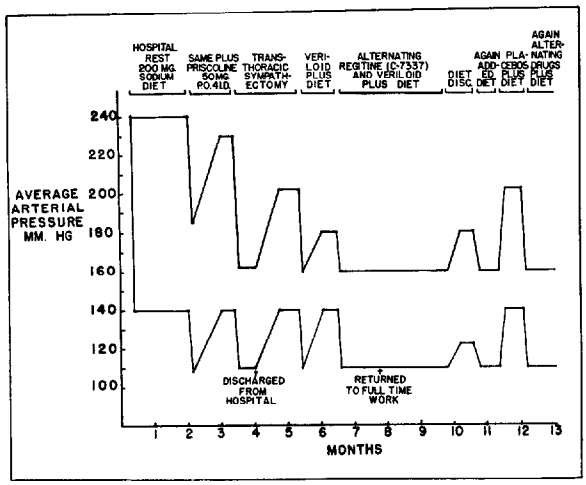

FIG. 3. Chart of the average arterial pressure (supine) and treatment of patient, H. F., a Negro aged 28 years. In each period the recorded level of arterial pressure represents the average of many readings. See text for further details.

to a trial of Veriloid, but an unusual and striking response to Priscoline by mouth 50 mg. 4 times per day. However, the response did not continue, and after a month tolerance to the drug became almost complete. A transthoracic sympathectomy was then performed with a good reduction in blood pressure, which again was not sustained. We again tried a low sodium diet and Veriloid with a good fall in arterial pressure, which also was only temporary.

* A product of Riker Laboratories, Los Angeles, Calif.

It then occurred to us that, since this patient exhibited satisfactory responses to both Veriloid and Priscoline for short periods and then exhibited tolerance to these drugs, we might forestall the development of tolerance by alternating the drugs at weekly intervals. Instead of Priscoline, we used a very similar drug called Regitine or C-7337. With this regimen tolerance did not develop and the average blood pressure during this period remained reduced. The patient has returned to work and is completely asymptomatic. The diet was discontinued for several weeks with moderate elevation of blood pressure levels, but more striking was the disappearance of postural hypotension. I have noted in several instances that patients who have had sympathectomies in years past frequently will exhibit a return of postural hypotension when salt is adequately restricted. When placebos were given in this case the general level of diastolic pressure returned to the original values but fell again to the treatment levels on resuming the alternating drug therapy.

In a series such as this it is always impressive to describe several of the more striking cases, but such a portrayal fails to give a true picture of the success of the treatment in the group as a whole. Since this study has been in progress for only a year the data are still in the process of being collected. Nevertheless, I am able to indicate in a rough way the results obtained to date at least in the patients given Anatensol, one of the extracts of Veratrum viride.

It should be remembered that these results pertain only to severe hypertensives. All in this group had diastolic pressures of 120 mm. Hg or greater even after 48 hours of rest in bed in the hospital. All had grade II to grade IV hypertensive changes in the fundi and 7 exhibited grade IV optic fundi, that is, malignant hypertension. In this entire group approximately half also are presumed to be taking the 200 mg. low sodium diet. Of this number, however, only 20 per cent are following their diet as judged by the excretion of urine chloride. None are on the rice diet. Two have had sympathectomies. I have avoided the use of the classification of excellent result since in no case has the blood pressure been reduced to normal and maintained there for a prolonged period. The duration of observation varies between 3 and 14 months, with an average duration of 8 months. A good result signifies that the average diastolic pressure has been reduced 20 mm. Hg or more as compared to pretreatment hospital blood pressures and that there has been symptomatic relief as well as some objective improvement either in the fundi, the heart size, or renal function. It also signifies that as judged by the use of placebo the greater part of this improvement was due to the Anatensol.

There are 32 patients in this group, of which 10 may be classified as a good result and 4 as a fair result. In addition there are 6 who had a good or fair result which was not sustained. However, 4 of these latter patients have exhibited a good result when Veriloid was substituted for Anatensol. Four patients cannot be classified because they failed to return for a follow-up, and 8 are judged complete failures. In general, the failures were due to an inability to regulate dosage without frequent toxic effects.

Although Veriloid seems to be the best of the veratrum extracts thus far produced, all of the veratrum derivatives including Veriloid are notoriously difficult to regulate over long periods of time. The reasons for this are as follows:

1. Varying dosage requirements in different patients necessitating individual adjustment in each case. One adjusts the dosage of Veriloid in much the same fashion as one would adjust the dose of insulin in a diabetic; that is, he regulates dosage by observing the response.

2. Varying sensitivity of the patient to a given dose. During therapy with veratrum there is considerable fluctuation in blood pressure from day to day although the average may be lower. In some of our most severe cases it has been necessary for a member of the family to check the blood pressure before each dose of the drug and regulate the dose up or down slightly according to the reading obtained.

3. Narrow margin between the dose which lowers blood pressure and that which produces side-effects. This is the most serious limiting factor of all. As a result side-effects are to be expected rather frequently in the adjustment period and occasionally thereafter. As with any potent drug which can produce toxic effects, the physician must decide between the advantages to be gained by treatment as weighed against the disadvantages and annoyances of frequent reactions. It is for this reason that I do not think the use of veratrum is justified in any but the most severe types of hypertension.

Far better results with fewer severe reactions have been obtained when the dosage has been regulated in hospitalized patients, and for this reason I have just about abandoned the idea of attempting to begin treatment with Veriloid as an outpatient or office procedure.

The method of adjusting dosage which has been found to be most successful is as follows: The patient is hospitalized for at least 48 hours prior to beginning therapy. The blood pressure is recorded 4 times per day in order to obtain a pretreatment baseline. Quite frequently in the hospital the blood pressure will fall to the benign range prior to treatment. Such patients are treated preferably symptomatically with sedation, rest periods, and reassurance. However, if the diastolic pressure remains elevated, treatment is begun with a dose of 2 mg. of Veriloid 4 times per day after each of 3 widely spaced meals and at midnight. The aim is to keep the interval between doses as close to 6 hours as possible. The purpose of this is to permit 1 dose to become effective as the other is losing its effect. If the doses are too far apart the blood pressure may rise between doses, and if they are too close together severe toxic reactions may occur due to overlapping of 1 dose on the other.

The blood pressure is recorded just before each dose and 2 hours after each dose except after the midnight medication. At the end of 48 hours the blood pressure chart is inspected and the patient questioned about the appearance of side-effects. The earliest common side-effects are epigastric or substernal burning sensation, epigastric fullness, and increased salivation. When these symptoms occur no further increase in dosage is undertaken for an additional 48 hours.

If there are no side-effects and no change in the blood pressure, the dose is increased to 3, 2, 2, and 3 mg. If this is ineffective at the end of an additional 48 hours, all of the doses are increased to 3 mg. In this way one gradually approaches the therapeutic dose, which usually varies between 3 and 4 mg. 4 times per day, that is, a total dose of 12 to 16 mg. per day, which may be higher or lower in individual cases. By this gradual increase toxic effects, while not completely avoided, are at least minimized.

After a therapeutic dose has been reached there frequently are mild side-effects in addition to a perceptible drop in blood pressure. During the ensuing weeks apparently a certain degree of cumulation occurs, since not infrequently nausea and vomiting or varying degrees of severe hypotension occur in the second to the fourth weeks of treatment.

Severe reactions are very alarming to both the physician and the patient. The nausea comes in waves for several hours and is accompanied by violent retching. A period of extreme hypotension and bradycardia may accompany this. Occasionally patients have lost consciousness for several minutes. This violent reaction has been mistaken for a coronary occlusion by those unfamiliar with the drug. When such a reaction occurs the patient should be given atropine 0.9 mg. (1/75th grain) intravenously, and if hypotension continues he may be given ephedrine 50 mg. intramuscularly. It is remarkable that despite these profound reactions no death or permanent disability has resulted. However, in advanced uremia extreme hypotension and vomiting may hasten the end. For this reason I no longer use veratrum or its derivatives when the blood nonprotein nitrogen is greater than 70 mg. per cent. The patient is told that when a reaction occurs he is to omit the next dose on that day only and on

succeeding days to reduce the offending dose by no more than a half-tablet amount. Nausea and vomiting may occur after other doses also, and in each case the offending dose should be reduced by a half-tablet amount. Occasionally nausea and vomiting may be due to the failure to take the tablets at the specified times and are taken too closely together. Therefore, it is well to inquire as to whether the meals are widely spaced and the tablets taken at the specified times.

After several months of treatment when the patient has apparently been satisfactorily regulated, the blood pressure reading may be higher than previously. It is well to remember that the blood pressure may fluctuate considerably on Veriloid therapy, and it is worthwhile to see the patient several times before changing the dose. If the arterial pressure remains high, one may cautiously raise the morning or the midnight dose by 0.5 mg. If there are no toxic effects, another of the doses may be raised by a similar small increment. This procedure is continued until the blood pressure falls or the patient develops toxic effects. If on this second trial nausea and vomiting occur without a fall in blood pressure, only then is one justified in considering the treatment a failure. Of course, in malignant hypertensives periodic reactions seem justified in view of the serious nature of the illness, if at the same time the blood pressure is maintained at a lower level.

In case of failure with veratrum alone it has been my policy to place the patient on a low sodium diet. This diet contains 200 mg. of sodium per day. It is very important either to omit milk completely since its sodium concentration is high or to use Lonalac, a salt-free milk powder which must be flavored with cocoa or powdered coffee to make it palatable. In addition salt-free bread which is available in many special food stores and unsalted butter must be used. Printed lists of this diet are available to interested physicians from the Mead Johnson Company. It has been my experience that the so-called salt-free diet prescribed in most hospitals is entirely inadequate for the purpose, since the sodium content is not sufficiently restricted.

Finally and most important is to determine the chloride content of the urine at regular intervals. This value should be at least below 0.6 Gm. of sodium chloride per liter of urine. If it is above this, the patient is not following the diet. In this series more than 75 per cent of patients treated failed to follow the diet as judged by the salt excretion in the urine, although all avowed they were living up to it faithfully. When confronted with the evidence that they were not keeping to the prescribed regimen a certain number returned to a fairly satisfactory salt-restricted diet. Because of this foible of human nature it is obvious that unless the urinary chloride excretion is followed during treatment with low-salt diets the physician is truly working in the dark.

If the 200 mg. sodium diet does not produce a satisfactory response, Veriloid may be tried again in conjunction with the diet, and it is surprising how effective these therapeutic regimens are when used together. During salt restriction many patients can be maintained on doses of Veriloid or Anatensol which are below the toxic level. In short, there appears to be a synergism between these methods of therapy in many patients.

If this combination treatment fails and if the patient is below the age of 50 with fairly good renal function I have resorted to sympathectomy. Usually in such severe cases the operation is inadequate in itself, but reinstitution of medical therapy following sympathectomy has in some instances produced a satisfactory, persistent, hypotensive response.

The so-called hypertensive "crisis" is a sudden and severe elevation of blood pressure associated frequently with acute hypertensive encephalopathy and can be fatal. It is best treated in the hospital. A very satisfactory method of treating this condition has been to administer immediately 3 mg. of Veriloid followed by 1 mg. every hour until the blood pressure begins to fall. Usually a total of 4 to 7 mg. is required to produce a hypotensive response. This may be repeated as often as is necessary on succeeding days, or, better still, the patient may be regulated on a maintenance dose of the drug.

HEXAMETHONIUM

During the past 6 months we have been studying the effects of the new ganglionic blocking agent, hexamethonium or C6,* in hypertension. Properly administered, this agent has produced significant and sustained reductions of arterial pressure in almost all hypertensive patients whom we have studied. In a series of 15 patients with malignant hypertension a remission of the malignant phase has occurred in 11 cases. The 4 patients who have not responded have all had advanced renal failure with uremia. Although hypotension was produced in these cases the uremia progressed and 3 have died. In less severe degrees of hypertension results have been almost uniformly satisfactory in that marked reductions of blood pressure have been produced.

It must be emphasized, however, that the drug was given by subcutaneous injection twice per day. It was also apparent that certain precautions, additions, and modifications in the treatment regimen are essential to obtain satisfactory results.

It was observed that whereas the hypotensive response to the initial dose of C6 may be profound, "tolerance" developed rapidly when the dosages were repeated at such frequent intervals as every 4 or 6 hours. However, when doses were separated by 12-hour intervals the development of tolerance was largely prevented. If under these circumstances the drug became ineffective, the hypotensive action could be restored by increasing the dosage. The average initial dose was 10 mg. of the ion, but after several weeks of continuous therapy the average effective dose was 35 mg. of the ion.

The duration of action of each dose varied between 4 and 12 hours or even longer. In general the postural hypotension outlasted the reduction in supine pressure, but in many patients the disease appeared to be modified while under continuous therapy in that with return to activity the levels of blood pressure throughout the 12-hour period remained lower than pre-treatment values. However, in the more severe cases the blood pressure levels fluctuated markedly over the 12-hour period between doses, from normal or nearly normal blood pressure values 1 hour after each dose to markedly hypertensive values immediately before each dose. Many of these patients could be controlled by administered L-hydrazinophthalozine (C-5968)† in doses of 50 to 150 mg. orally midway between doses of C6. In a few patients it was possible to maintain a satisfactory reduction of blood pressure by administering C6 at 8-hour instead of 12-hour intervals.

Like all agents which block transmission through the sympathetic nervous system C6 induces a marked postural hypotension. After the initial injection of the drug patients may faint on arising for as long as 3 hours after the drug has been administered. However, with continued administration of the drug the postural hypotension, although still marked, becomes no longer profound. Hence, after the first week of treatment the majority of patients can assume the upright position without postural giddiness 1 hour after the drug has been given and many can arise immediately. Since the night dose is given at bedtime, only the morning injection produces temporary physical incapacity in some patients.

Since hexamethonium also produces parasympathetic blockade, certain side-effects have arisen due to this action of the drug. The most common have been dry mouth due to reduction in the secretion of the salivary glands and constipation due to atony of the gastrointestinal tract. The most serious reactions have been paralytic ileus and inability to micturate. All of these side-effects can be overcome by the concurrent administration of the urethane of acetyl-methylcholine (Urecholine) in doses of 10 mg. under the tongue 3 times per day. Moderate constipation may persist in some patients despite the use

* Bistrium obtained from The Squibb Institute for Medical Research, New York, N. Y.

† A product of CIBA Pharmaceutical Products, Inc., Summit, N. J.

of Urecholine, but the constipation can be managed by mild laxatives.

Just as sodium restriction increases the hypotensive effect of other drugs, a diet low in sodium will increase the patient's responsiveness to C6. Hence, in occasional resistant cases sodium restriction has been used in addition.

Because of the marked hypotension produced by the initial injection of C6 certain precautions must be observed in beginning dosage administration. Severe hypotensive reactions have been avoided since we have utilized the following technic for beginning therapy: With the patient propped up slightly in bed, C6 is injected intravenously at a rate of 1 to 2 mg. of the ion per minute. An assistant determines the blood pressure at intervals of 30 seconds in the opposite arm. As soon as a significant reduction of blood pressure occurs the injection is halted temporarily until the blood pressure becomes stabilized. If the degree of hypotension is satisfactory, the injection is stopped; if not, the slow rate of administration is begun again and continued until the desired result is obtained. If, despite these precautions, the reduction of blood pressure is excessive, it may be easily corrected by raising the foot of the bed on 6-inch or 8-inch blocks and elevating and passively exercising the lower extremities. Vasopressor agents, especially epinephrine, are unpredictable, and impressed us as being dangerous.

Having determined the initial effective dose, this amount is administered subcutaneously at 12-hour intervals. At the end of 48 hours it is usually necessary to increase the dosages by 5 to 10 mg. and continue to increase them until the patient exhibits a sustained response.

The early results obtained with oral administration have been disappointing. Large doses are required, and there has been some evidence of cumulation as well as of tolerance. In addition, the bromide and iodide salts of hexamethonium are unsuitable for oral use, since the large doses required lead to toxic levels of these halides in the circulation. However, it may well be that a suitable dosage schedule using less toxic salts of C6 may be evolved with further experimentation. Preliminary evidence suggests that doses of 0.5 to 1.0 Gm. of C6 ion administered at bedtime every 24 hours (one dose per day) may produce satisfactory results. In addition, the bitartrate, dichloride or citrate salts of C6 may be used instead of the bromide or iodide salts.

In our experience of the past 6 months no form of treatment of essential hypertension has so profoundly altered the levels of blood pressure in such a large percentage of hypertensive patients as has the use of hexamethonium. Patients have been taught to administer their own injections and even record their blood pressures in the home. Many patients have returned to their usual occupations and because of the postural hypotension seem to be protected from blood pressure elevations due to physical and emotional stress.

It is possible by improper administration of C6 to obtain poor therapeutic results and dangerous toxic reactions; and, indeed, our early experiences with this agent were disappointing because of improper dosage administration. Further experience with this and other similar agents should bring additional improvements in the ease of administration and circumvention of side-effects. There is every reason to believe, however, that the chemotherapy of essential hypertension has been greatly improved by the introduction of hexamethonium.

In conclusion, these experiments in therapy are interesting, but it should be emphasized that they are not of proven long-term value. The reduction of blood pressure by any of the methods employed, whether by surgery, diet or the presently available hypotensive agents, apparently is nonspecific. Whether or not such nonspecific reduction of blood pressure actually will prolong life in these severe cases only time and continued observation can tell. It would be a mistake, therefore, to assume on the basis of our present knowledge that mere reduction of blood pressure is proof that our treatments actually delay the progression of the disease.